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SYSTEMATIC REVIEW

A Systematic Review of Economic Evaluation Methodologies Between Resource-Limited and Resource-Rich Countries: A Case of Rotavirus Vaccines

Kittiphong Thiboonboon[1] · Benjarin Santatiwongchai[1] · Varit Chantarastapornchit[1] · Waranya Rattanavipapong[1] · Yot Teerawattananon[1]

Abstract

Background For more than three decades, the number and influence of economic evaluations of healthcare interventions have been increasing and gaining attention from a policy level. However, concerns about the credibility of these studies exist, particularly in studies from low- and middle- income countries (LMICs). This analysis was performed to explore economic evaluations conducted in LMICs in terms of methodological variations, quality of reporting and evidence used for the analyses. These results were compared with those studies conducted in high-income countries (HICs).

Methods Rotavirus vaccine was selected as a case study, as it is one of the interventions that many studies in both settings have explored. The search to identify individual studies on rotavirus vaccines was performed in March 2014 using MEDLINE and the National Health Service Economic Evaluation Database. Only full economic evaluations, comparing cost and outcomes of at least two alternatives, were included for review. Selected criteria were applied to assess methodological variation, quality of reporting and quality of evidence used.

Results Eighty-five studies were included, consisting of 45 studies in HICs and 40 studies in LMICs. Seventy-five percent of the studies in LMICs were published by researchers from HICs. Compared with studies in HICs, the LMIC studies showed less methodological variety. In terms of the quality of reporting, LMICs had a high adherence to technical criteria, but HICs ultimately proved to be better. The same trend applied for the quality of evidence used.

Conclusion Although the quality of economic evaluations in LMICs was not as high as those from HICs, it is of an acceptable level given several limitations that exist in these settings. However, the results of this study may not reflect the fact that LMICs have developed a better research capacity in the domain of health economics, given that most of the studies were in theory led by researchers from HICs. Putting more effort into fostering the development of both research infrastructure and capacity building as well as encouraging local engagement in LMICs is thus necessary.

Key Points for Decision Makers

Economic evaluations are becoming popular and are being used in low- and middle- income countries (LMICs), reflecting the need for local evidence. However, most of the studies in LMICs were not conducted by local researchers.

Limitations in some methodological areas of economic evaluations in LMICs were identified, nonetheless, overall, the quality of economic evaluations in LMICs is fairly good.

There is a need to develop local capacity to conduct economic evaluations in LMICs instead of only adopting studies conducted by non-local researchers.

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✉ Kittiphong Thiboonboon
kittiphong10@gmail.com

[1] Health Intervention and Technology Assessment Program, Department of Health, Ministry of Public Health, 6th Floor, 6th Building, Tiwanon Road, Muang, Nonthaburi 11000, Thailand

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1 Introduction

Economic evaluations are used to assess the value for money of new interventions, i.e. comparing the resources used and health consequences of introducing a new technology as a tool for more efficient allocation of health resources, which are limited [1]. As healthcare expenditures are growing, economic evaluations play a vital role in many countries to determine whether any intervention should be included for reimbursement [2]. A high volume of this type of empirical research is published each year, which indicates the importance of economic evaluations [3]. However, it should also be emphasised that economic evaluations will be useful for informing health policy decision making only when performed correctly and reported accurately.

Researchers face several challenges, both methodological and contextual, when conducting economic evaluations [4, 5]. Based on well-established academic and economic situations, producing economic evaluations in high-income countries (HICs) may be facilitated with systematic support. However, this may not be the case in low- and middle- income countries (LMICs) where several limitations exist in terms of financial support, qualified researchers, reliable data sources and country-specific methodological guideline for economic evaluation [6–9]. These limitations create challenges for conducting economic evaluations, which raise issues on the quality of economic evaluation, especially in LMICs. As such, the methods used for the conduct of economic evaluations are regularly cited as a weakness that diminishes the quality of economic evaluations [10].

The rotavirus causes health problems in very young people and ranges from mild illness to severe diarrhoea and death. Approximately half a million infants and children aged under 5 years die annually in LMICs as a result of rotavirus disease [11]. The first preventive human vaccine for rotavirus infections was RotaShield®, which was licensed in 1998. Unfortunately, it was discovered that the vaccine may have contributed to an increased risk for intussusceptions and was subsequently withdrawn from the market in 1999 [12]. Currently, two rotavirus vaccines are distributed at a global level, namely RotaRix® (RV1) and RotaTeq® (RV5) [13], while at least two local brands produce the vaccine, Lanzhou Lamb® and RotaVac®, which are used in China and India respectively [14].

Systematic reviews and meta-analyses of trials across several settings suggest that both vaccines are effective and the level of efficacy between RV1 and RV2 is not significantly different [13, 15]. For example, the number of cases with rotavirus diarrhoea among vaccinated children could be reduced by 72 % compared with 73 % by using RV1 and RV5, respectively [13]. Similarly, another meta-analysis of post-introduction of vaccine studies has shown the overall estimate of the relative risk of rotavirus vaccine-associated intussusception for RV1 was 5.4 for the first dose and 1.8 for the second dose compared with 5.5 (first dose) and 1.7 (second dose) for RV5 [16]. Rotavirus vaccines are relatively expensive compared with other traditional childhood vaccines. To support the distribution of vaccines, the Global Alliance for Vaccines and Immunization (GAVI) provides financial support to certain countries so that they can introduce these vaccines into their national immunisation programmes. As of 2016, 81 countries, including in Europe and North America, have offered universal rotavirus vaccination for children aged less than 5 years [17].

A review of the quality of economic evaluations can offer invaluable inputs to improve the quality of future studies. This may also be beneficial for those in other settings who do not have the capacity to conduct primary research on their own. The objective of this literature review is to explore the variability of economic evaluations in LMICs in terms of methodology, quality of reporting and quality of evidence used by comparing them with studies in HICs. This review focuses on one particular intervention, rotavirus vaccines, to enable a reasonable comparison of characteristics across studies. The intervention was selected on the basis of the high level of interest in the value for money of the rotavirus vaccine, which is reflected in the considerable number of published economic evaluations conducted in both resource-rich and resource-poor settings [18].

2 Methods

2.1 Search Strategies

Economic evaluations of rotavirus vaccines were identified using MEDLINE and the National Health Service Economic Evaluation Database (NHS EED). The search was performed in March 2014 with no time constraints for publication date. The search terms "(cost OR cost benefit OR cost effectiveness OR cost utility OR economic evaluation OR decision analysis) AND (rotavirus OR rotavirus vaccine OR rota vaccine)" were used for MEDLINE and "rotavirus" was used for the NHS EED. The full search strategies can be seen in electronic supplementary material (ESM) Appendix 1.

2.2 Selection of Studies

Two authors (KT and BS) screened the search results and identified potential relevant articles via titles and abstracts. The texts of the articles were then assessed independently

for inclusion from the shortlisted pieces using the following criteria: (1) full economic evaluations, comparing costs and consequences of two or more policy options; (2) original studies, not editorials or updated versions; and (3) articles published in English.

2.3 Data Extraction and Analysis

For each study that met the selection criteria, data were extracted by BS, VC, WR and YT into a data sheet and independently cross-checked by KT. The extracted characteristics of reviewed studies are presented in ESM Appendix 2.

2.4 Classifying Country-Income Groups

The settings of studies were identified and classified according to the 2012 World Bank criteria [19]. The countries are classified as high income when their gross national income per capita is US$12,616 or more. Countries with a gross national income per capita of US$12,615 or less are classified as LMICs. The affiliation of the first author was observed to indicate local research capacity. This relies on the assumption that the first author was a person leading the study. To do so, the location of the first author's affiliated institution was used to determine the settings where the studies were produced instead of using their homeland or country of residence.

2.5 Assessment Criteria

Although we used rotavirus vaccine economic evaluations to highlight the differences in methodology and quality owing to their abundance in both settings, the true aim of the review is to assess studies in general and not for disease-specific issues. Therefore, most of the technical criteria used in this study were generic and applied commonly used indicators for evaluating the characteristics and quality of economic evaluations. Included studies were investigated for three areas: the variations of methods used, the quality of reporting and the quality of evidence used.

First, to explore the methodological variations of the economic evaluations, this review considered different types of economic evaluations, outcome measures, study perspectives, modelling approaches, time horizons, discount rates for both costs and outcomes, and types of uncertainty analysis.

Second, in terms of quality of reporting, the included studies were appraised with adherence to the most recently updated Consolidated Health Economic Evaluation Reporting Standards checklist [20], a specific reporting guideline consolidating a number of guidelines into one standard. Prior to starting the review, it was expected that many economic evaluations would be retrieved from the search and owing to the limited timeframe for review, only those items from the checklist that could be applied in a straightforward manner and judged clearly were selected. The criteria include: (1) clearly indicating the study perspective; (2) clearly describing the comparator(s) being compared; (3) reporting the approach used for the decision-analytical model; (4) clearly stating the time horizon(s) over which the costs and consequences are being evaluated; (5) clearly indicating cost discounting; (6) clearly indicating outcome discounting; (7) reporting the dates of the estimated resource quantities and unit costs; (8) describing methods for adjusting estimated unit costs to the year of reported costs if necessary; (9) providing a figure of the model structure; (10) reporting the values, ranges, references and, if used, probability distributions for all parameters; (11) reporting the incremental cost-effectiveness ratio; (12) disclosing funding sources; and (13) describing any potential conflicts of interest of the authors.

Last, the final part observed was the quality of evidence used to estimate parameters for the models and was assessed using hierarchies for data sources in economic analyses as used by Cooper et al. [21] in the UK and later employed by Teerawattananon et al. [8] in Thailand. The components of the hierarchy of quality for data sources, which offered a way of assessing the quality of evidence used, are: (1) the clinical effect size (vaccine efficacy); (2) baseline clinical data, e.g. incidence rate of rotavirus infection and number of rotavirus-associated inpatient and outpatient visits; (3) costs; and (4) utilities if the evaluation is a cost-utility analysis. An explanation of the scoring system is shown in Table 1.

3 Results

3.1 Studies Included in the Analysis

A total of 710 records were identified from the search. After adjusting for duplicates, 626 records remained. Of these, 530 records were discarded after screening the titles and abstracts. The remaining 96 studies were reviewed thoroughly for eligibility. During this process, one potentially relevant study was found from the references of the articles and was added to the shortlist, thereby increasing the number to 97 papers. From the review, 12 studies were then excluded, which consisted of five review papers, two updated manuscripts of rotavirus economic evaluations studies and five non-economic evaluations. Finally, 85 studies met the inclusion criteria and were included in the systematic review (Fig. 1).

Table 1 Hierarchies for data sources (reproduced from Cooper et al. [21])

Rank	Data components
	Clinical effect sizes
1+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes
1	Single RCT with direct comparison between comparator therapies, measuring final outcomes
2+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes
	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
2	Single RCT with direct comparison between comparator therapies, measuring the surrogate outcomes
	Single placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
3+	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes
3	Single placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes for each individual therapy
4	Case control or cohort studies
5	Non-analytic studies (e.g. case reports, case series)
6	Expert opinion
9	Not clearly stated
	Baseline clinical data (if applicable)
1	Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest
2	Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest
3	Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction
4	Old case series or analysis of reliable administrative databases. Estimates from RCTs
5	Estimates from previously published economic analyses: unsourced
6	Expert opinion
9	Not clearly stated
	Costs
1	Cost calculations based on reliable databases or data sources conducted for specific study: same jurisdiction
2	Recently published cost calculations based on reliable databases or data course: same jurisdiction
3	Data source not known: same jurisdiction
4	Using charge (price) rather than cost when societal perspective was adopted
5	Recently published cost calculations based on reliable databases or data sources: different jurisdiction
6	Data source not known: different jurisdiction
9	Not clearly stated
	Utilities (if applicable)
1	Direct utility assessment for the specific study from a sample either:
	(a) of the general population, or
	(b) with knowledge of the disease(s) of interest, or
	(c) of patients with the disease(s) of interest
	Indirect utility assessment from specific study from patient sample with disease(s) of interest, using a tool validated for the patient population
2	Indirect utility assessment from a patient sample with disease(s) of interest, using a tool not validated for the patient population
3	Direct utility assessment from a previous study from a sample either:
	(a) of the general population, or
	(b) with knowledge of the disease(s) of interest, or
	(c) of patients with the disease(s) of interest
	Indirect utility assessment from previous study from patient sample with disease(s) of interest, using a tool validated for the patient population
4	Data source not known: method of elicitation unknown
5	Patient preference values obtained from a visual analogue scale
6	Delphi panels, expert opinion
9	Not clearly stated

RCT randomised controlled trial

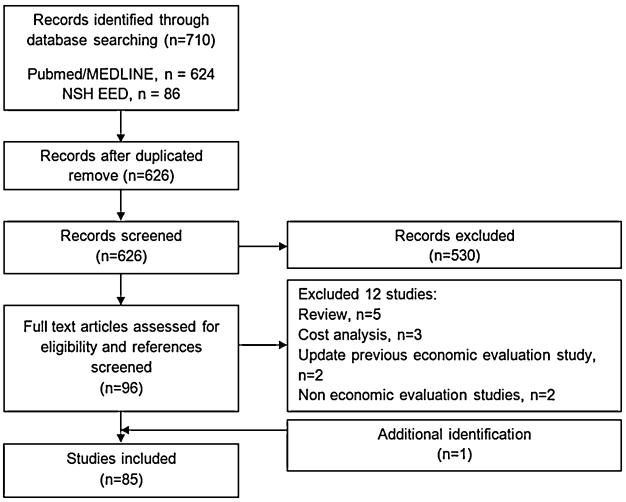

Fig. 1 Search result of the literature review. *NSH EED* National Health Service Economic Evaluation Database

3.2 General Features of the Studies

3.2.1 Study Setting and Year of Publication

Almost the same number of economic evaluation studies was found between HICs (45 papers; 53 %) and LMICs (40 papers; 47 %). The first two papers were published for HICs in 1995 even before the first rotavirus vaccine was registered in the market [22, 23], while the first two papers focusing on LMICs were published in 2005 [24, 25]. The number of publications peaked after the GAVI recommendation in 2006 to introduce the rotavirus vaccines into the Expanded Program on Immunization [26] and the World Health Organization (WHO) in 2009 [27] (Fig. 2).

3.2.2 Study Interventions

There were 25 studies (29 %) that evaluated rotavirus vaccines without specifying the trade name, 23 studies (27 %) evaluated both RotaRix® and Rotateq®, 18 studies (21 %) evaluated RotaRix® alone and 17 studies (20 %) solely evaluated Rotateq®. All but one study (1 %) used 'no vaccination' as a study comparator, while the remaining one did not state anything. It is interesting to note that HICs were more interested in learning which type of rotavirus vaccine represented better value for money, whereas LMICs were more interested in learning whether any type of rotavirus vaccine provided value for money.

3.2.3 Settings of First Author Affiliations

Most of the first authors of included studies were from institutions located in HICs and accounted for 88 % of the studies analysed (75 of 85 studies). Despite the fact that all

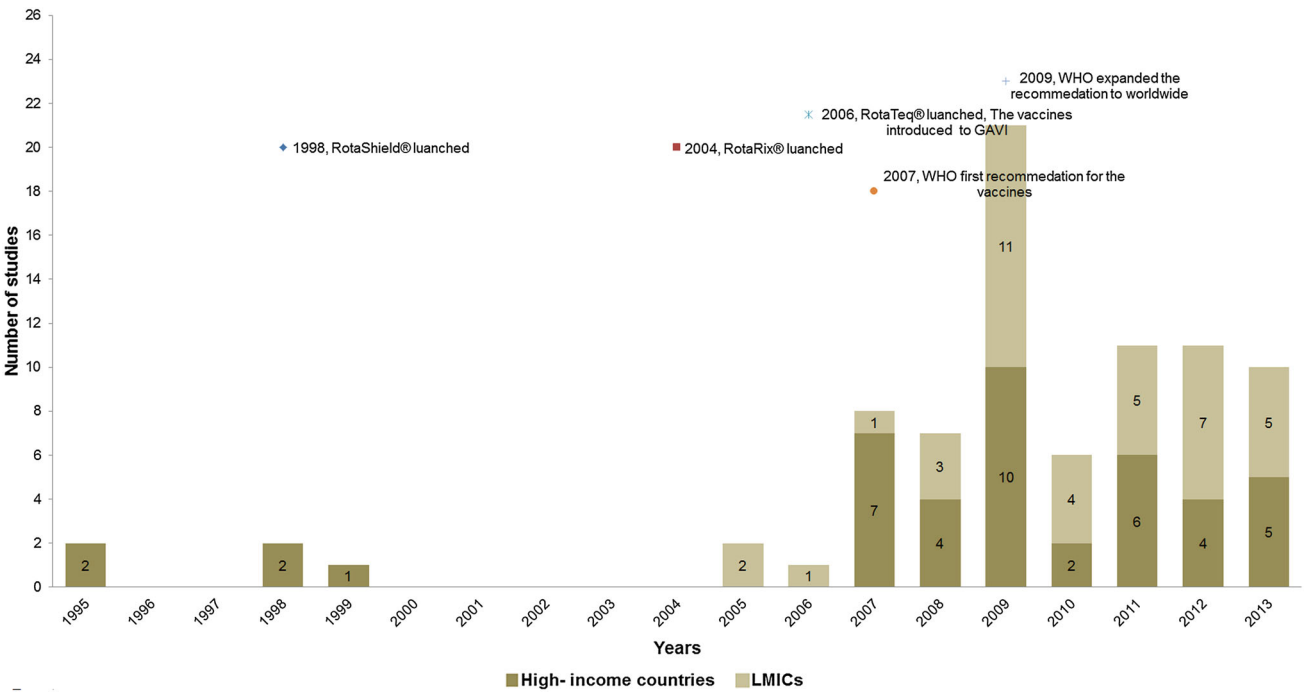

Fig. 2 Number of economic evaluations of rotavirus vaccines and related important events published in English per year from 1995 to 2013. For year 2014, up to March 2014, there were two publications in HICs and one study in LMICs. *GAVI* Global Alliance for Vaccines and Immunization, *HICs* high-income countries, *LMICs* low- and middle-income countries, *WHO* World Health Organization

of the HIC studies were conducted by researchers affiliated to institutions from HICs, only 10 of the 40 LMIC studies (25 %) were conducted by researchers affiliated with institutions in LMICs. The majority of studies, 25 and 26 studies (56 and 65 %), were conducted by researchers in academic institutions in HICs and LMICs, respectively, and 13 studies of HICs (29 %) and 13 studies of LMICs (33 %) were conducted by public health organisations. The remaining studies were conducted by pharmaceutical companies, including one study in LMICs and seven studies in HICs.

3.2.4 Methodological Variations

Table 2 illustrates the different methodologies used in the studies. Cost-utility analysis is the most popular approach, accounting for 80 % of the studies in LMICs and 60 % of the studies in HICs. Disability-adjusted life year (DALYs) is the preferred choice for measuring outcomes among studies in LMICs whereas the quality-adjusted life-year is more common among studies in HICs. While the societal viewpoint accounts for about half of studies in LMICs (48 %), it was adopted in most studies in HICs (82 %). A Markov model was often used for estimating costs and outcomes of the vaccinations in HICs (40 %). However, in LMICs, 50 % of the studies did not specify their modelling approach well and 38 % of the studies used a decision tree; few studies conducted in LMICs and HICs applied dynamic models for estimating costs and outcomes of vaccinations. It is clear that most studies in both settings used a 5-year time horizon. Most studies applied a 3 % discount rate for both cost (83 % of studies in LMICs and 67 % of studies in HICs) and outcome measures (78 % of studies in LMICs and 59 % of studies in HICs), while nine studies applied a lower rate of discounting outcome (Fig. 3), and among these nine studies, eight studies (89 %) were HIC studies. In both settings, almost all studies in LMICs (97 %) and HICs (98 %) performed some form of uncertainty analysis. Of these, half of the studies (53 % in each setting) applied univariate sensitivity analysis and one-third of the studies (35 % in LMICs and 29 % in HICs) performed a probabilistic sensitivity analysis with a univariate or multivariate uncertainty analysis.

Most variables show that there are variations in the methodology used between these two settings. Among these, the most obvious variables are the outcomes measured and approach of modelling, as well as discounting rates for cost and outcome. There is no difference in the choices of the methods used for studies conducted in LMICs between those with the first author's affiliation in the study setting and those with the first author's affiliation outside the study setting.

3.2.5 Quality of Reporting

Table 3 demonstrates that, in general, both settings are fairly good for reporting standards. As can be seen from the 13 listed items, the LMICs did well in eight areas with over 80 % of the evaluated studies stating the assigned criteria while the HIC studies did well in nine of them. However, it is apparent that HIC studies had relatively higher reporting standards than those of LMICs. This is particularly evident for the description of approaches and the model illustrations used (50 and 48 % of the study in LMICs vs. 96 and 67 % of the study in HICs). The most omitted information from the economic evaluation papers is the potential conflict of interest between co-authors and the funding sources supporting the study. This item was provided in about only half of the studies conducted for both LMICs (43 %) and HICs (53 %). It is interesting to note that studies in both settings did not describe their methods well for cost-time adjustment when using costing studies that were conducted in the past (68 % in LMICs and 62 % in HICs). This is similar to stating the funder, in which only 68 and 58 % of the included studies of LMICs and HICs, respectively, described this item. Taking into account the first author's affiliation, the studies conducted in LMICs with the first author affiliated with the institute in the study setting are more likely to report the types of model used and potential conflicts of interest than those studies with the first author affiliated with the institute outside the study setting. However, the studies with the first author affiliated with the institute in the study setting are less likely to report the method of cost-time adjustment and detail model parameters than the studies with the first author affiliated with the institute outside the study setting.

3.2.6 Quality of Evidence Used

Table 4 and Fig. 4 illustrate that HIC studies used better quality evidence for economic models compared with LMIC studies. This is apparent in the baseline clinical data, costs and utility categories where HICs have a higher ratio of studies using data specifically analysed for the economic evaluations (24 vs. 8 %, 42 vs. 23 % and 11 vs. 0 % in HICs vs. LMICs for baseline clinical data, costs and utility, respectively), while most studies in LMICs relied on unspecific analyses or previously published literature. Regarding clinical effect sizes, a few studies (5 %) in HICs applied a meta-analysis to calculate effectiveness of the vaccines for their model, whereas most of the studies in both settings used information only from single, placebo-controlled, randomised controlled trials (95 % in LMICs vs. 93 % in HICs). Expert opinion was used in two of the LMIC studies conducted for baseline clinical data and in one study for estimating clinical effect sizes. The quality of evidence used for utility estimation is also lower for studies

Table 2 Summary of different methodologies used in economic evaluations of the rotavirus vaccine in HICs and LMICsVariables

	HICs		LMICs		LL		LH	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Economic evaluation types								
CEA	14	31	7	18	4	40	3	10
CBA[a]	4	9	1	3			1	3
CUA	27	60	32	80	6	60	26	87
Main outcome measured								
Case averted (e.g. hospitalisations averted, deaths averted)	12	27	2	5	1	10	0	0
Life-year gained	2	4	5	13	3	30	2	7
Monetary benefit	4	9	1	3			1	3
QALYs	24	53	2	5			2	7
DALYs	3	7	30	75	6	60	24	83
Study perspective								
Third-party payers	1	2	1	3	1	10		
Healthcare system	4	9	11	28	1	10	10	33
Public government/provider	3	7	5	13	2	20	3	10
Societal	37	82	19	48	6	60	13	43
Not specified			4	10			4	13
Approach of modelling								
Decision tree	13	29	15	38	5	50	10	33
Markov	18	40	3	8	1	10	2	7
Decision tree and Markov			1	3	1	10	0	0
Dynamic model	2	4	1	3			1	3
Other types of models	8	18						
Non-modelling technique, e.g. economic evaluation alongside trials	2	4						
Not specified	2	4	20	50	3	30	17	57
Time horizon								
1 year	1	2						
2 years	1	2	2	5	1	10	1	3
3 years	1	2						
5 years	30	67	33	83	7	70	26	87
7 years	2	4						
10 years	1	2						
14 years			1	3			1	3
20 years	3	7	1	3			1	3
50 years	1	2						
Lifetime	5	11						
Not specified			3	8	2	20	1	3
Cost discounting								
No discount	3	7	1	3	1	10		
1.5 %	1	2						
3.0 %	27	59	31	78	5	50	26	87
3.5 %	5	11						
4.0 %	4	9						
5.0 %	5	11						
6.0%			1	3	1	10		
Not specified	1	2	7	18	3	30	4	13

Table 2 continued

	HICs		LMICs		LL		LH	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Outcome discounting								
No discount	4	9						
1.5 %	6	13						
2.0 %	1	2						
3.0 %	20	43	35	88	6	60	29	97
3.5 %	5	11						
4.0 %	3	7						
5.0 %	5	11	1	3	1	10		
6.0 %		0	1	3	1	10		
Not specified	2	4	3	8	2	20	1	3
Types of uncertainty analysis								
Univariate analysis alone	24	53	21	53	4	40	17	57
Multivariate analysis alone	2	4	1	3			1	3
Univariate and multivariate	5	11	3	8	1	10	2	7
PSA and univariate or multivariate	13	29	14	35	5	50	9	30
Not performed	1	2	1	3			1	3

CEA cost-effectiveness analysis, *CBA* cost-benefit analysis, *CUA* cost-utility analysis, *HICs* high-income countries, *LH* LMIC studies led by non-local author (HICs), *LL* LMIC studies led by local author (LMICs), *LMICs* low- and middle-income countries, *QALYs* quality-adjusted life-year, *DALYs* disability-adjusted life-year, *PSA* probabilistic sensitivity analysis

[a] There were two studies; one from LMICs that used DALYs and another from a HIC that used QALYs as the health outcome. However, their main outcome was monetary. Therefore, we justified them as CBA

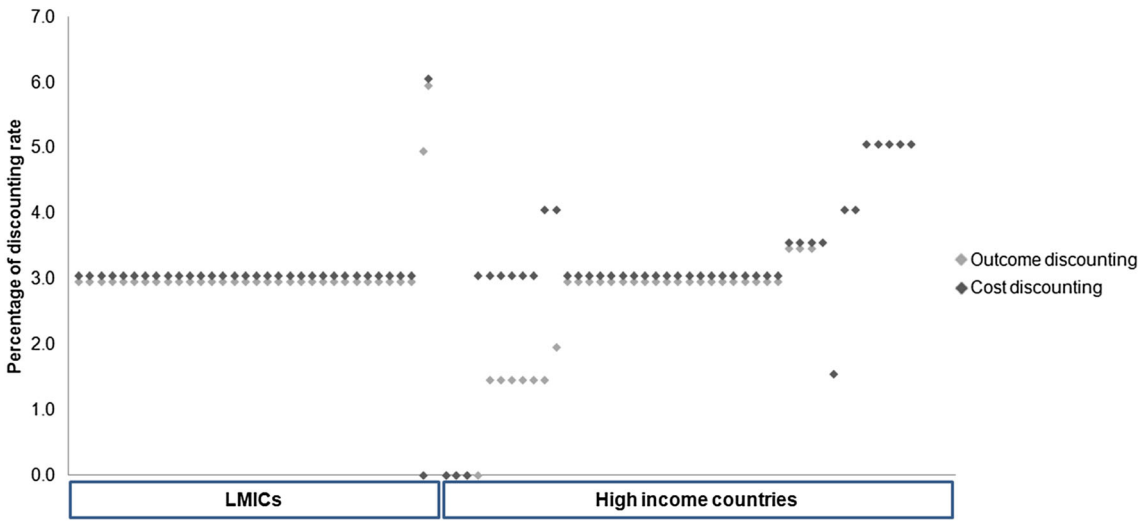

Fig. 3 Diagram illustrating a higher variation of cost and outcome discounting used in economic evaluations of rotavirus vaccines in HICs compared with LMICs. Only studies stating both cost and outcome discounting were selected. *HICs* high-income countries, *LMICs* low- and middle-income countries

in LMICs because most of them employed DALYs as a utility measure, which resulted in grade 3, the default for studies that adopt disability weight derived from the WHO Global Burden of Disease. For studies conducted in LMICs, the primary data collection is often used for cost estimation where the first author is affiliated with the institute in the study setting whereas the secondary sources, including from different jurisdictions, are the preferable choice for studies where the first author is affiliated with the institute outside the study setting.

Table 3 Quality of reporting assessment in economic evaluation publications of rotavirus vaccines

Item no.	Criteria	HICs [*n* (%)]	LMICs [*n* (%)]	LL [*n* (%)]	LH [*n* (%)]
1	Perspectives described	45/45 (100)	36/40 (90)	10/10 (100)	26/30 (87)
2	Comparator(s) described	45/45 (100)	39/40 (98)	10/10 (100)	29/30 (97)
3	Model type described	43/45 (96)	20/40 (50)	7/10 (70)	13/30 (43)
4	Time horizon described	45/45 (100)	37/40 (93)	8/10 (80)	29/30 (97)
5	Cost discounting described	44/45 (98)	33/40 (83)	7/10 (70)	26/30 (87)
6	Outcome discounting described	43/45 (96)	37/40 (93)	8/10 (80)	29/30 (97)
7	Price date described	37/45 (82)	39/40 (98)	9/10 (80)	30/30 (100)
8	Method of cost-time adjusting explained	28/45 (62)	27/40 (68)	5/10 (50)	22/30 (73)
9	Figure of model used shown	29/43 (67)	19/40 (48)	5/10 (50)	14/30 (47)
10	Model parameter reported	42/45 (98)	34/40 (85)	6/10 (60)	28/30 (93)
11	ICER reported	38/45 (84)	36/40 (90)	8/10 (80)	28/30 (93)
12	Funder described	26/45 (58)	27/40 (68)	7/10 (70)	20/30 (67)
13	Conflict of interest declared	24/45 (53)	17/40 (43)	6/10 (60)	11/30 (37)

ICER incremental cost-effectiveness ratio, *HICs* high-income countries, *LH* LMIC studies led by non-local author (HICs), *LL* LMIC studies led by local author (LMICs), *LMICs* low- and middle-income countries

4 Discussion

The review suggests there are a high number of economic evaluations of rotavirus vaccine in both LMICs and HICs, revealing substantial consideration given to this intervention. For the three key areas investigated, the review observed that there is a potential dissimilarity in preferred methodological choices of economic evaluations between these two settings. The review also pointed out a difference in the level of evidence used in the analysis among the settings. However, both settings have a reasonable quality level of reporting study results.

The review found a relatively low variation in the methods used among studies conducted in LMICs compared with that of methods used in HICs. Differences are observed in the selection of DALYs over other outcome measures, adopting a 3 % discounting rate for both costs and outcomes, using a decision tree model and applying a 5-year time horizon. The selection of these approaches could be partly explained by the aspect of disease complications that are expected to occur within a short period of time; thus, a simple model (decision tree or 5-year time horizon) might be appropriately adopted [28]. The low variation in the methods used is also reflected in the lack of national methodological guidelines for conducting economic evaluations in these settings, resulting in the use of the WHO's guideline for conducting cost-effectiveness analysis [29] in many studies, which was reflected in the application of the 3 % discount rate and the use of DALYs. In addition, there is an important implication from the discounting rates applied in the included studies. As discount rates can lead to different results and affect healthcare resource allocation [30], HICs are therefore keen to opt for the rates more suitable and applicable to their settings. However, studies in different LMICs apply the same discount rate, which might be done only to fulfil the standard methodology requirement. Other possible implications of differences in methodology on the presented cost-effectiveness results include: (1) the static model that was applied by most of the included studies is not capable of accounting for the benefit of the existence of indirect protection effects associated with the vaccine [31]; (2) many of the included studies use a 5-year time horizon, and, in technical aspects of extrapolation, this will not be able to capture the outcome of patients alive at the end of 5 years [1]; and (3) while differences in discount rates will really affect the result of the model with a long time horizon, for a time horizon of 5 years, which was used by most of the included studies, differences in discount rates are rather unlikely to have a large impact on the results, except when there is substantial mortality.

There are noticeable differences in the methodologies used between LMICs and HICs. It should be emphasised that the review did not intend to inform about methodological preferences or accurateness, e.g. Markov model over decision tree, societal perspective over provider's perspective, or quality-adjusted life-years over DALYs. However, there may be an interesting point about the systematic asymmetry of methodological variations between studies on the very same intervention conducted in low- vs. high-resource settings, as well as whether the choice of methods used in LMICs was based on scientific reasoning. One of the shortfalls is the shortage of

Table 4 Quality of evidence used in economic evaluations of rotavirus vaccines

Hierarchy of evidence	Clinical effect sizes [*n* (%)]				Baseline clinical data [*n* (%)]				Costs [*n* (%)]				Utility [*n* (%)]			
	HICs	LMICs	LL	LH	HICs	LMICs	LL	LH	HICs	LMICs	LL	LH	HICs	LMICs	LL	LH
1 +																
1					11 (24)	3 (8)	1 (10)	2 (7)	19 (42)	11 (29)	4 (40)	7 (23)	3 (11)			
2+																
2	2 (5)				19 (42)	17 (44)	5 (50)	12 (40)	21 (47)	13 (34)	4 (40)	19 (63)	3 (11)			
3+	40 (93)	38 (95)	9 (90)	29 (97)												
3					3 (7)	6 (15)	2 (20)	4 (13)	1 (2)	1 (3)		1 (3)	17 (61)	26 (79)	5 (83)	21 (78)
4					10 (22)	9 (23)	1 (10)	8 (27)	1 (2)				3 (11)	1 (3)		1 (4)
5					1 (2)	1 (3)		1 (3)	3 (7)	13 (34)	1 (10)	12 (40)				
6		1 (3)	1 (10)			2 (5)		2 (7)								
9	1 (2)	1 (3)		1 (3)	1 (2)	1 (3)	1 (10)	1 (3)			1 (10)	1 (3)	2 (7)	6 (18)	1 (17)	5 (18)

ICs high-income countries, *LH* LMIC studies led by non-local author (HICs), *LL* LMIC studies led by local author (LMICs), *LMICs* low- and middle-income countries

methodological guidelines that are tailored to the context of LMICs. A good example of this type of guideline is the Gates reference case, which provides a set of methodological specifications to which researchers in LMICs can easily adhere [32].

Most of the included studies had a good quality of reporting. This may be because the study focused on published literature in international journals that were already screened for quality, usually through offered checklists or standard formats for reporting [33]. However, it should be noted that half of the studies that were conducted in LMICs did not provide sufficient information on the model used. When the type of model was not well described, it might cause difficulty in validating data used in the model, e.g. transitional probability. Although in some cases it is possible to extract the model types as well as the health state diagram from the text, it is suggested that the choice of model and its related aspects should be clearly defined. At the least, authors should address the choice of model, rationale of the model selection, as well as the figure of the model. Additionally, despite the fact that issues around conflicts of interest and the role of funders have been raised and regularly suggested in many checklists, this type of information was poorly reported in both settings. Given that many studies reported an economically attractive result, it is important to consider the association of these results with commercial biases.

Regarding the quality of evidence used, a higher quality was found in all types of input parameters used in HIC studies when compared with LMIC studies. While HICs used data from meta-analyses of randomised controlled trials or a single randomised controlled trial to estimate clinical effect sizes, a few studies conducted in LMICs deployed expert opinion or did not clearly elaborate on the data sources for the same parameters. For baseline clinical data, costs and utility parameters, studies in HICs often used data collected specifically for the studies, whereas LMICs used previously published data from either local or international sources. This difference could be explained by accessibility problems as well as availability of data. Accessibility problems might be linked to the profile of investigators of LMIC studies as most of them are foreigners and thus it may be difficult for them to access local sources for primary data; local involvement is therefore of high importance in terms of obtaining and accessing data. Data availability might be associated with several limitations such as the shortage of reliable administrative databases [34].

For studies conducted in LMICs, our sub-group analysis showed there were small differences in the methods used and the quality of evidence and reporting between the studies with the first author affiliated with the institute in the study setting and the studies with the first author

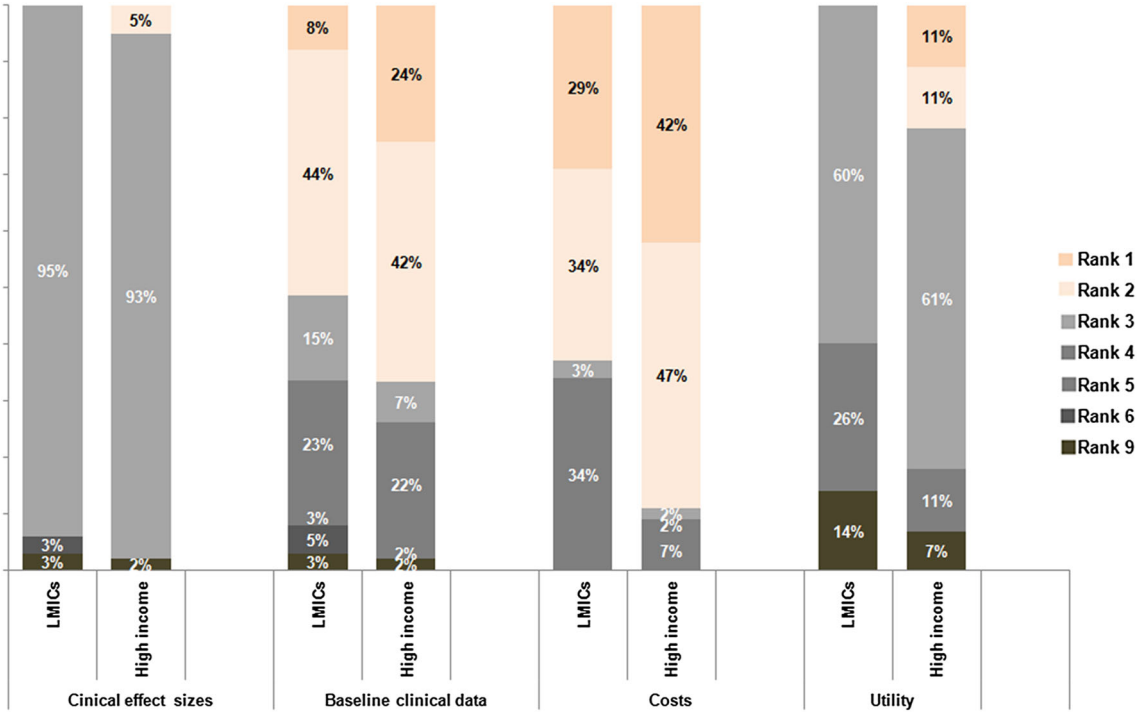

Fig. 4 Quality of evidence used in economic evaluations of rotavirus vaccines. *LMICs* low- and middle-income countries

affiliated with the institute outside the study setting. Although it is understandable that the studies with the first author affiliated with the institute in the study setting are more likely to use primary data sources for costing because of local knowledge and accessibility to local data sources, in-depth exploration may be needed into the differences in other aspects such as the difference in declaring conflicts of interest. Moreover, these results should be viewed with caution given the low number of studies with the first author affiliated with the institute in the study setting.

The findings of this analysis confirm the results of a previous review that the quality of economic evaluations in resource-limited settings are inferior compared with resource-rich countries [27]. Nevertheless, there is an obvious change in a positive way for the quality of economic evaluations in LMICs when comparing our review with earlier economic evaluation studies in developing countries [35, 36]. For instance, in 2000, Walker and Fox-Rushby [35] found that of all the included studies, only 23 % indicated their perspective and 43 % performed a sensitivity analysis, while the proportions were 90 and 98 %, respectively, in this study. Again, this could be the result of substantial efforts to promote and improve the quality and transparency of economic evaluations through a number of checklists and guidelines for economic evaluations. The previous two reviews of economic evaluations of rotavirus vaccines were published in 2011 [37] and 2013 [38]. The former review identified only studies in developing countries while the latter included all economic evaluations regardless of country income level. These two studies did not emphasise the determination of the quality of the studies, as the adherence to technical criteria was not intensively assessed. However, the studies mentioned similar issues that were found in this review such as a shortage of local evidence in LMICs, e.g. epidemiological data in particular.

While there is a considerable number of studies in LMICs compared with HICs, based on the assumption that the first author of a publication is the person who led the project, it is important to note that three-fourths of the studies in LMICs were conducted by principal investigators from HICs. This implies that the capacity for conducting economic evaluations remains concentrated in resource-rich settings. Although the rotavirus vaccine offers large health benefits to children living in LMICs, many LMICs are not able to provide value-for-money arguments to support vaccine adoption. As the number of studies conducted in LMICs have been increasing after the GAVI's and the WHO's recommendations to include the vaccine in the Expanded Program on Immunization, this may be owing to LMICs governments' need for local information to support their decision rather than simply following the recommendations. Thus, our findings suggest that international donors need to, aside from providing financial support for the vaccine, invest more on capacity building for economic evaluation studies, which is the issue that has

been frequently emphasised elsewhere [39–41]. This is to ensure the availability of locally relevant and timely information for decision makers who need to determine whether to adopt new and high-cost vaccines.

There are some limitations in this review. First, this study intended to compare differences in methodological choice, reporting of quality and evidence used in conducting economic evaluations between LMICs and HICs, using a number of economic evaluations on rotavirus vaccines as a case study. Selection of the rotavirus case provides benefit to this review in at least two aspects: (1) the high number of studies makes it more sensible for comparison; and (2) choosing only a single disease and intervention will remove heterogeneity that may occur compared with choosing or sampling different diseases or interventions. However, the results of this study may not be easily extrapolated to other diseases or interventions as there are some features that tend to be specific to the type of diseases or interventions. For example, the choice for a particular model is related to the characteristics of a disease and its complication, and assessing the effectiveness of the intervention depends on the availability of rotavirus vaccine trials. However, most of the criteria are general technical issues and should be applicable to other diseases or interventions.

Second, this study included only English literature despite the fact that some studies [42–45] published in languages other than English were identified in our search. Nevertheless, compared with the 85 available studies, there were only four non-English publications, thus it should not affect the results of this study.

Third, because the study included only published literature, it is possible that there is literature such as local government reports that was not published in journals, particularly researchers in LMICs where the ability to publish is limited owing to uncontrollable factors such as economic constraints. As a result, the included published literature from LMICs may reflect the better quality literature of these LMICs and the review may therefore overestimate the quality of LMIC studies, as low-quality reports have not been published.

Fourth, it may not be appropriate to include and compare studies from different periods of time, given that there might be time-related differences in the quality of economic evaluations. Notwithstanding, the majority of studies were conducted after 2005 or within the last decade, which means that it is still a reasonable comparison.

Fifth, instead of using a statistical test such as logistic regression analysis, descriptive comparison is used to report the results of this review. However, this simple form of reporting results may limit a reader's ability to infer whether or not there are true differences in the findings between LMICs and HICs.

Last, as the initial aim of the review was to highlight technical aspects used in economic evaluations and to inform and assist the future development of economic evaluations in LMICs rather than to focus on specific issues or attributes of the rotavirus and vaccines as well as model validation, explorations into several important characteristics of the disease and vaccines such as the plausibility of value of parameters of incidence, efficacy or cost of vaccines were not exhaustively investigated, evaluated and reported in this study. However, it should be noted that these parameters could be problematic, thereby crucially affecting the quality of the study.

5 Conclusion

Focusing on the case of rotavirus vaccines, while HIC studies have a reasonable standard of economic evaluations, the evidence in LMICs is of a lower quality. Although this study found a high number of economic evaluations of rotavirus vaccines in LMICs, most of these studies were published by researchers from HICs. This indicates that LMICs may not have improved in terms of research capacity in health economics. The development of research infrastructure and capacity building in LMICs, as well as local involvement in the study process, are therefore still necessary.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest and financial interests.

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